Xenon does not reduce opioid requirement for orthopedic surgery

[Le xénon ne réduit pas les besoins d'opioïdes en chirurgie orthopédique]

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Purpose: Is to test the hypothesis that 70% xenon has a relevant opioid sparing effect compared to a minimum alveolar concentration (MAC)-equivalent combination of N_2O and desflurane.

Methods: In this randomized, controlled study of 30 patients undergoing major orthopedic surgery, we determined the plasma alfentanil concentration required to suppress response to skin incision in 50% of patients (Cp_{50}) anesthetized with xenon (70%) or a combination of N_2O (70%) and desflurane (2%). A response was defined as movement, pressor response > 15 mmHg, heart rate > 90 beats·min^{-1}, autonomic reactions or a combination of these. At skin incision, alfentanil was administered at a randomly selected target plasma concentration thereafter the concentration was increased or decreased according to the patient's response. After skin incision, desflurane was adjusted to maintain the bispectral index below 60 and prevent responsiveness in both groups.

Results: The Cp_{50} (± standard error) of alfentanil was 83 ± 48 ng·mL^{-1} with xenon and 49 ± 26 ng·mL^{-1} with N_2O/desflurane (P = 0.451). During surgery five xenon and 15 N_2O/desflurane patients were given desflurane at 1.0 ± 0.5 volume % and 2.5 ± 0.7 volume %. The total age adjusted MAC was 0.97 ± 0.07 and 0.94 ± 0.07 respectively (P = 0.217). The intraoperative plasma alfentanil concentrations were 95 ± 80 and 93 ± 60 ng·mL^{-1} respectively (mean ± SD; P = 0.451). Patients given xenon were slightly more bradycardic, whereas blood pressure was similar.

Conclusion: Xenon compared to a MAC-equivalent combination of N_2O and desflurane does not substantially reduce opioid requirement for orthopedic surgery. A small but clinically irrelevant difference cannot be excluded, however.

Objectif : *Vérifier l'hypothèse voulant que le xénon à 70 % permette de réduire significativement les opioïdes en comparaison d'une combinaison équivalente de concentration alvéolaire minimale (CAM) de N_2O et de desflurane.*

Méthode : *L'étude randomisée et contrôlée comptait 30 patients devant subir une intervention orthopédique majeure. La concentration plasmatique d'alfentanil nécessaire pour supprimer la réaction à une incision cutanée chez 50 % des patients (Cp50) sous anesthésie au xénon (70 %) ou une combinaison de N_2O (70 %) et de desflurane (2 %) a été déterminée. Une réaction était un mouvement, une réponse vasopressive > 15 mmHg, une fréquence cardiaque > 90 battements·min^{-1}, des réactions autonomes ou une des réactions combinées. Lors de l'incision cutanée, l'alfentanil était administré selon une concentration plasmatique cible choisie aléatoirement, et la concentration augmentée ou diminuée selon la réaction du patient. Après l'incision, le desflurane était ajusté pour maintenir l'index bispectral en bas de 60 et éliminer les réactions chez tous les patients.*

Résultats : *La Cp50 (± erreur type) de l'alfentanil a été de 83 ± 48 ng·mL^{-1} avec le xénon et de 49 ± 26 ng·mL^{-1} avec N_2O/desflurane (P = 0,451). Pendant l'opération, cinq patients sous xénon et 15 sous N_2O/desflurane ont reçu du desflurane à 1,0 ± 0,5 volume % et 2,5 ± 0,7 volume %. L'ajustement total de la CAM en fonction de l'âge a été de 0,97 ± 0,07 et de 0,94 ± 0,07 respectivement (P = 0,217). les concentrations plasmatiques d'alfentanil ont été de 95 ± 80 et de 93 ± 60 ng·mL^{-1} respectivement (moyenne ± écart type ; P = 0,451). Les patients qui ont reçu du xénon ont présenté un peu plus de bradycardie, mais la tension artérielle était similaire entre les groupes.*

Conclusion : *Le xénon, comparé à une CAM d'une combinaison équivalente de N_2O et de desflurane, ne réduit pas significativement les besoins d'opioïdes en orthopédie. On ne peut toutefois exclure une petite différence, mais cliniquement non significative.*

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MORE than ten years ago Lachmann and co-workers detected a fivefold reduction of the fentanyl requirement for general surgery in patients anesthetized with 70% xenon compared to those anesthetized with 70% nitrous oxide (N_2O) in oxygen.[1] These results triggered a number of subsequent studies documenting the fast induction and emergence kinetics[2] and the cardiovascular stability of xenon.[3,4] Xenon was also suggested as a potential alternative to N_2O because it is not teratogenic.[5] A recent randomized, controlled, multicentre study showed that anesthesia with xenon is safe and provides a more rapid recovery than isoflurane with N_2O.[6]

Although it is not surprising that the patients in the study by Lachmann and co-workers[1] receiving one minimum alveolar concentration (MAC) of xenon required less fentanyl than the patients receiving 0.7 MAC of N_2O, the difference was far greater than expected from the difference in MAC. Because of its weak hypnotic effect N_2O (with a MAC-awake of 63%)[7] must be supplemented by a potent volatile or *iv* anesthetics to prevent awareness.[8] The insufficient hypnosis of the N_2O patients might, therefore, have biased Lachmann's study. We defined a control group where a sufficient depth of hypnosis would be ascertained by adding small concentrations of desflurane to N_2O. Adding 2.8 volume % of desflurane to 60% N_2O corresponds to 1 MAC in middle-aged subjects.[9] Assuming the two agents are additive, we considered 70% N_2O plus 2 volume % desflurane as MAC-equivalent to 70% xenon.[10] Because the MAC-awake of xenon is 33%,[7] we considered 70% xenon sufficiently hypnotic.

Given the large opioid sparing effect of xenon reported by Lachmann and co-workers[1] we hypothesized that opioid requirements would be lower in xenon anesthetized patients even if control patients were given a MAC-equivalent combination of N_2O/desflurane. We determined the alfentanil plasma concentration required to suppress the response to skin incision in 50% of patients (Cp_{50}) and the median alfentanil concentration necessary to suppress response to intraoperative surgical stimulation in patients anesthetized with 70% xenon or N_2O supplemented with desflurane to maintain the bispectral index (BIS) level below 60 and to prevent responsiveness.

Methods

With approval of the local Ethical Committee and written informed consent, we recruited 30 ASA physical status I and II patients scheduled for elective orthopedic surgery. Patients were stratified[11] according to age and type of surgery and randomly assigned to either xenon or N_2O plus desflurane (N_2O/desflurane) anesthesia. Patients with diabetes mellitus; any relevant renal, liver, heart (including arterial hypertension), neurological, or psychiatric disease; a regular alcohol consumption of more than 20 g per day,[12] drug abuse; or taking sedatives or long acting analgesic drugs were excluded. Additional details on the methods are available as Additional Material at www.cja-jca.org.

Study plan

Thirty minutes after premedication with 7.5 mg midazolam *po* the patients were monitored with a Datex AS3 monitor and an Aspect A1000 BIS monitor (BIS version 3.2, Aspect Medical Systems, Inc., Newton, MA, USA). Anesthesia was induced with 2.5 $mg \cdot kg^{-1}$ propofol, 1 $\mu g \cdot kg^{-1}$ remifentanil, and 0.1 $mg \cdot kg^{-1}$ vecuronium to facilitate tracheal intubation. After induction, desflurane was administered at 3 volume % and an arterial catheter was inserted into the radial artery of the non-dominant arm. A computer-controlled infusion of alfentanil was started at a randomly selected alfentanil target plasma concentration between 5 and 400 $ng \cdot mL^{-1}$ (Stanpump program, pharmacokinetic parameters for alfentanil by Raemer *et al.*[13] software freely available from S.L. Shafer, M.D., Palo Alto, CA, USA). The study gas (either 70% N_2O or xenon) was then started (at least 15 min before Cp_{50}) and desflurane was eliminated by use of a charcoal filter in the xenon group whereas it was reduced to 2 volume % in the N_2O group. The maximal systolic blood pressure, heart rate, and any motor reaction within five minutes of skin incision were recorded. During surgery the xenon and N_2O concentrations were kept constant at 70 volume % whereas the target plasma alfentanil concentration was increased by 25 to 50 $ng \cdot mL^{-1}$ if the patient showed any response to incision as defined below. Conversely alfentanil was decreased by 25 $ng \cdot mL^{-1}$ if the patient did not show any response to the surgical stimulation during the last 20 min. The maximal target alfentanil concentration allowed was 500 $ng \cdot mL^{-1}$. The patient's responsiveness to verbal command was checked every 20 min (isolated forearm technique). To prevent awareness and recall desflurane was adjusted in steps of 0.5 volume % in order to maintain the BIS below 60 and to prevent responsiveness. Desflurane was therefore allowed also in the xenon group as a rescue drug, if the patient was responsive or if the BIS increased above 60 for longer than four minutes.[14]

A response to skin incision or to intraoperative surgical stimulation was defined as a motor response, a blood pressure increase of more than 15 mmHg above

baseline, a heart rate increase above 90 beats·min^{-1} in the absence of hypovolemia, an autonomic response (such as tearing, sweating, or flushing) or a combination of these.[15] Baseline systolic blood pressure was defined as the average of measurements taken on the ward the day before surgery and in the operating room before induction.

All the data from the Datex AS3 monitor, the Aspect A1000 and a Dräger thermal conductivity sensor measuring the xenon concentration[16] were recorded on a computer disk.

At baseline, immediately before and at five minutes after skin incision, and before and two to five minutes after each change of the target alfentanil concentration during surgery, an arterial blood sample was withdrawn for determination of the alfentanil plasma concentration. Blood samples for alfentanil measurement were immediately centrifuged at 3500 g for 30 min and the plasma stored at -26°C. Alfentanil plasma concentration was measured by gas chromatography mass spectrometry.[17]

On the second day after surgery a blinded investigator interviewed the patients for signs of explicit recall.

Data analysis and statistics

The alfentanil concentration to suppress patient response to skin incision was computed by logistic regression for the two study groups using NONMEM software (Sheiner LB, Beal SL: NONMEM user's Guide 1994, University of California San Francisco, CA, USA). For the intraoperative period the median of the plasma alfentanil concentrations measured between skin incision and closure and the median alfentanil infusion rate was determined.

According to Ausems *et al.*[15] the CP_{50} ± standard error (SE) of alfentanil to suppress response to Cp_{50} is 279 (20) ng·mL^{-1} (n = 37) in a mixed population and to suppress an intraoperative response in breast surgery 270 ± 63 ng·mL^{-1} in patients anesthetized with N_2O in oxygen without potent volatile anesthetics. With 15 subjects per group, we expected to detect a difference of 50 ng·mL^{-1} between groups with a power of > 0.80 (one tailed t test).

The number of blood pressure recordings greater than 20% or below 20% of baseline, the number of heart rate recordings above 90 min^{-1} or below 20% of baseline and the number of episodes with BIS > 60 for longer than four minutes were determined for each subject.[18]

Data were compared with a Student's t test or a Wilcoxon rank test as appropriate. Results are presented as means ± SDs or number of patients, unless otherwise noted. $P < 0.05$ was considered significant.

Results

The characteristics of the two study groups were similar (Table I).

Response to skin incision

Two patients in each group were excluded from the analysis because the desflurane concentration accidentally differed more than 20% from the target value. The train-of-four count at Cp_{50} was four twitches in every subject. The Cp_{50} for alfentanil was 83 ± 48 ng·mL^{-1} in the xenon group and 48 ± 25 ng·mL^{-1} in the N_2O/desflurane group (parameter estimate ± SE, P = 0.451; Figure 1).

Response during surgery

All 15 patients of each group were included in the analysis. The median plasma alfentanil concentration

TABLE I Characteristics of the study population

	Xenon	*N_2O/desflurane*	*P value*
Men/women	7/8	9/6	0.49
Age; yr	32 ± 6	33 ± 11	0.60
Weight; kg	69 ± 14	72 ± 16	0.53
Height; cm	172 ± 6	172 ± 12	0.62
BMI*	23 ± 4	24 ± 4	0.35
ASA status (I/II)	14/1	12/3	0.59
Baseline systolic pressure; mmHg	124 ± 13	121 ± 11	0.54
Type of surgery			
Hip dislocation	11	9	0.70
Periacetabular osteotomy	3	4	1.0
Low back surgery	1	2	1.0
Duration of surgery; min	151 ± 60	136 ± 28	0.42

Data presented as mean ± SD or number of patients. N_2O = nitrous oxide; *BMI = body mass index.

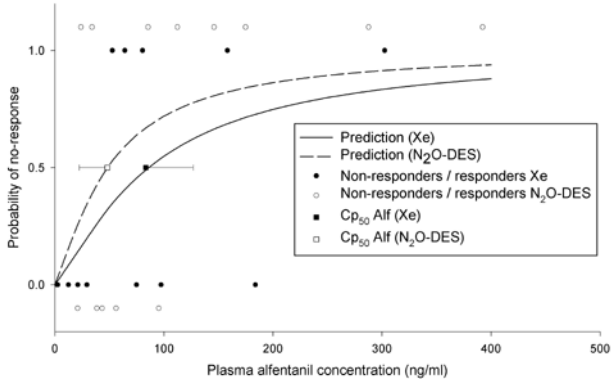

FIGURE 1 The predicted probability of no-response to skin incision (Cp_{50}) is plotted in relation to the measured plasma alfentanil concentration. Responders and non-responders of the xenon group are represented by filled circles and those of the nitrous oxide (N_2O)-desflurane group by open circles. The filled and open squares represent the Cp_{50} of alfentanil in the xenon and the N_2O/desflurane group respectively (error bars = standard error of the estimate).

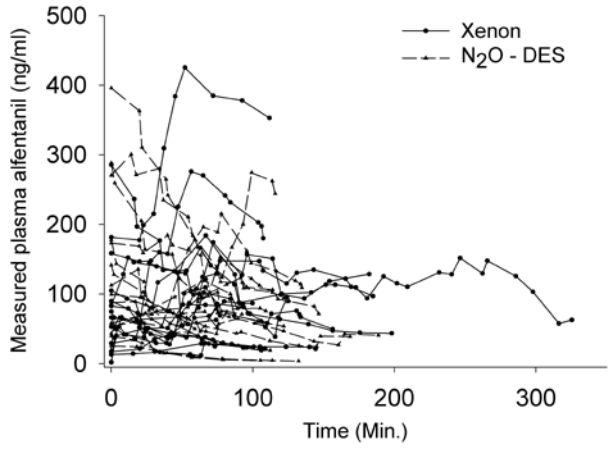

FIGURE 2 The measured plasma alfentanil concentrations between skin incision and closure are plotted for each subject. Solid lines with filled circles = xenon patients, dashed lines with triangles = nitrous oxide (N_2O)/desflurane patients.

during surgery and the median alfentanil infusion rate to prevent intraoperative response was similar in the two groups (Table II). Five of 15 patients were given desflurane (1.0 ± 0.4 volume %) in addition to xenon because of a sustained BIS increase > 60 (four subjects) and uncontrollable blood pressure increase despite 500 ng·mL^{-1} of alfentanil (one subject). In these patients the mean (SD) BIS level was 46 (8) and the median alfentanil concentration was 111 (127) ng·mL^{-1}. In xenon patients without desflurane the mean (SD) BIS level was 36 (8) and the median alfentanil concentration was 86 (49) ng·mL^{-1} ($P = 0.075$ for BIS, $P = 0.58$ for alfentanil). In the patients undergoing hip arthrotomy with surgical dislocation of the hip[19] the median alfentanil concentration during surgery was 100 (39) ng·mL^{-1} in the N_2O/desflurane and 96 (92) ng·mL^{-1} in the xenon group ($P = 0.92$). Excluding the three xenon patients of this subgroup who were given desflurane, the median alfentanil concentration during surgery was 82 (54) ng·mL^{-1} ($P = 0.43$ compared to the N_2O/desflurane patients).

No patient responded to verbal command during surgery. One patient in the N_2O/desflurane group experienced awareness with recall during tracheal intubation because of a failure of desflurane supply before administration of the study gas.[20]

Discussion

In a previous study xenon, compared to N_2O, was associated with a reduction of fentanyl requirement by far exceeding the difference in MAC of the two gases.[1] In contrast, our data do not show a relevant reduction of alfentanil requirements to suppress hemodynamic, autonomic or motor responses to Cp_{50} in xenon patients compared to those receiving a MAC-equivalent combination of N_2O and desflurane. There was no difference in the alfentanil infusion rate and the mean measured alfentanil concentration during surgery even though the BIS level was lower in the xenon patients. The anesthetic regimens provided similar hemodynamic stability except for a higher incidence of bradycardia in the xenon group and a lower arterial pressure in the N_2O/desflurane group. Xenon as the main anesthetic does not have an opioid sparing effect compared to a MAC-equivalent combination of N_2O and desflurane.

Suppression of motor response to skin incision (MAC) has been the gold standard to measure the potency of anesthetics. It reflects mainly a spinal reflex independent of the anesthetic drug concentration in the brain, however.[21] This is illustrated by the fact that the BIS did not predict movement response to insertion of a laryngeal mask.[22] It is therefore not surprising that the BIS levels in the two study groups were different even though the *post hoc* calculation of age-adjusted total MAC was similar. If xenon had a true opioid-sparing effect, the alfentanil concentrations to suppress response to painful surgical stimulation

TABLE II Hemodynamic responses, anesthetic gas concentrations and BIS level

	Xenon	*N_2O/desflurane*	*P value*
Desflurane at skin incision (vol %)	0.10 ± 0.09	1.9 ± 0.1	< 0.001
BIS reading at skin incision	34 ± 10	55 ± 11	< 0.001
Gas concentration (vol %)	70.7 ± 1.3	70.1 ± 0.6	0.101
Desflurane during surgery (vol %)*	1.0 ± 0.4	2.5 ± 0.7	0.002
MAC during surgery†	0.97 (0.06)	0.94 (0.07)	0.22
BIS reading during surgery	40 ± 10	54 ± 4	< 0.001
Median alfentanil plasma conc. ($ng \cdot mL^{-1}$)‡	95 ± 80	93 ± 60	0.95
Median alfentanil rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)‡	0.47 (0.30–0.63)	0.38 (0.36–0.55)	0.455
SAP; mmHg‡	128 ± 12	114 ± 10	0.002
SAP > upper limit (%)‡§	10.4 (3–13.5)	0.3 (0–8)	0.005
SAP < lower limit (%)‡¶	4.6 (4.1–6.1)	4.4 (3.9–26.2)	0.772
HR; $beats \cdot min^{-1}$‡	54 ± 6	59 ± 9	0.117
HR > upper limit (%)‡	0 (0–0.2)	0 (0–0.5)	0.868
HR < lower limit (%)‡¶	93 (66–99)	51 (15–92)	0.031

Data presented as mean ± SD or medians (inter-quartile range) as appropriate. *Calculated from the subjects given desflurane: five in the xenon group, 15 in the N_2O/desflurane group; †Age-adjusted total MAC (study gas + desflurane); ‡During surgery; §Systolic pressure upper limit = 15 mmHg above baseline; ¶Lower limit = 20% lower than baseline; Heart rate upper limit = 90 $beats \cdot min^{-1}$. BIS = bispectral index; N_2O = nitrous oxide; MAC = minimum alveolar concentration; SAP = systolic arterial pressure; HR = heart rate.

would have been smaller even at a MAC-equivalent concentration. The difference in BIS level can be explained by the weak sedative effect of N_2O, which does not affect BIS.[23] The BIS is a validated tool to measure depth of sedation with various *iv* and inhalation anesthetics; among them N_2O plus desflurane[24] but not xenon. The BIS did not predict responsiveness to verbal command at emergence of xenon anesthesia.[25] The deeper BIS levels in the xenon patients are therefore difficult to interpret and may not necessarily indicate a deeper hypnosis. Whatever the lower BIS levels mean, hemodynamic response and alfentanil requirements were not affected. Because of this uncertainty, desflurane was administered in four xenon patients because of a persistent BIS increase. Also, in these patients, alfentanil requirements were similar to those not given desflurane.

A xenon MAC of 71%[26] was the basis for the potency calculations for our study; however, in a recent study a MAC of 63% was reported for xenon.[27] The 70% xenon we used did not only produce significantly lower BIS levels, but might even have been more potent than the combination of 70% N_2O and 2% desflurane. Although this would suggest that the xenon patients would require less alfentanil they did not. Assuming a potency ratio of 1:70 between alfentanil and fentanyl,[28] the plasma alfentanil concentration to prevent response to skin incision in our study (83 $ng \cdot mL^{-1}$ in the xenon and 49 $ng \cdot mL^{-1}$ in the N_2O/desflurane group) was in the same range as the value reported for fentanyl (0.94 $ng \cdot mL^{-1}$).[29]

The limitation of our primary sample size calculation was that it had to be based on data from a study with a somewhat different design (e.g., N_2O without volatile anesthetics). Compared to previous studies on alfentanil requirements to suppress motor and hemodynamic response to Cp_{50} or intraoperative surgical stimuli[15,30] we observed substantially greater standard deviations of our Cp_{50} values. A *post hoc* power analysis revealed that 15 subjects per group would allow detecting a difference between groups greater than 125 $ng \cdot mL^{-1}$ for Cp_{50} and greater than 80 $ng \cdot mL^{-1}$ for intraoperative alfentanil requirements with a power greater than 0.8. Our Cp_{50} of alfentanil were below 100 $ng \cdot mL^{-1}$ in both groups and thus far below the Cp_{50} for naloxone requirement of 223 (13) $ng \cdot mL^{-1}$ reported by Ausems *et al.*[15] In order to reach sufficient power to detect a difference of 50 $ng \cdot mL^{-1}$ as many as 150 patients per group would have been necessary. Due to the small sample size we therefore might have missed a small opioid sparing effect of xenon but we can exclude a substantial difference as reported by Lachmann and co-workers.[15] In view of the high cost of this inhalation anesthetic a small difference would not be clinically relevant, however.

Using a stratified randomization protocol, the type of surgery was well balanced between the two groups (Table I). In the subgroup analysis of patients undergoing surgical dislocation of the hip (11 in the xenon and nine in the N_2O/desflurane group) alfentanil requirements were not significantly different, even when the three xenon patients who were given desflu-

rane are excluded. Even highly standardized conditions (one standardized operation) did not allow to detect a clinically relevant and statistically significant opioid sparing effect of xenon.

The definition of a response was previously used by Ausems and co-workers[15] and is closest to clinical practice, where motor response, hemodynamic response or autonomic signs of inadequate anesthesia are also considered together for dosing anesthetic drugs.

Because of the uncertainty of the BIS as a measure of hypnotic depth during xenon anesthesia[15] we additionally used the isolated forearm technique for clinical assessment of responsiveness. Since the duration of tourniquet inflation was similar in both groups (corresponding to the similar top-up doses of vecuronium), we assume that a potential hemodynamic response to tourniquet inflation would have been similar in both groups. One patient from the N_2O/desflurane group reported awareness and recall in the postoperative interviews.[20] This episode was well before the first study period and actually not related to the administration of the study gas.

Cardiovascular stability in our healthy patients anesthetized with a combination of N_2O and desflurane was similar than in those anesthetized with xenon. Low concentrations of desflurane, as applied in our study, sufficient to maintain a BIS of 40 to 65, were administered successfully in patients with inoperable coronary artery disease with a mean ejection fraction of 49%.[31] Despite the negative inotropic effect of desflurane, the ability of the heart to respond to increased preload was preserved in patients with a mean ejection fraction of 53% undergoing coronary surgery.[32] Thus, the true clinical utility of xenon justifying its cost remains open to question. Eventually, an ongoing study in patients with poor cardiovascular function may demonstrate some advantage of xenon over conventional anesthetics or its unique neuroprotective effect[33,34] detected in animal studies will be more important.

We conclude that alfentanil requirements and hemodynamic stability in healthy patients anesthetized with xenon and a MAC-equivalent combination of N_2O and desflurane are similar.

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